IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiffs, v. NATERA, INC., Defendant.	)	C.A. No. 19-567 (CFC) (CJB) CONSOLIDATED **JURY TRIAL DEMANDED**

NATERA, INC'S FIRST AMENDED COMPLAINT

Natera, Inc. ("Natera") submits this First Amended Complaint against CareDx, Inc. ("CareDx"), amending the Complaint filed in C.A. No. 20-038-CFC-CJB on January 13, 2020. Natera hereby alleges as follows:

NATURE OF THE ACTION

1. Natera brings this claim for patent infringement to compel CareDx to stop infringing Natera's patents and to compensate Natera for CareDx's blatant infringement of Natera's patented technology.

2. Founded in 2004, Natera (f.k.a Gene Security Network) is a pioneering genetics and bioinformatics company with industry-leading diagnostics products. Natera is dedicated to improving disease management for reproductive health, oncology, and organ transplantation. For well over a decade, Natera has been researching, developing, and commercializing non-invasive methods for analyzing DNA in order to help patients and doctors manage diseases. These ongoing efforts have given rise to a number of novel and proprietary genetic testing services to assist with life-saving health management.

3. Natera's pioneering and ongoing innovation is especially evident in the area of cell-free DNA ("cfDNA")-based testing. In the cfDNA field, Natera has developed unique and highly optimized cfDNA-based diagnostic methods that can be used to non-invasively test for a range of conditions. Natera developed an industry-leading cfDNA test, Panorama, which showcases its mastery of cfDNA in the field of non-invasive prenatal diagnostics. It is considered the industry leading test in this space, with over two million tests performed commercially, and with more than twenty-six peer-reviewed publications. Natera has also applied its cfDNA platform to the challenge of assessing organ transplant rejection. Natera's cfDNA testing methods are simpler and less invasive than traditional biopsy methods used to evaluate transplant health, and also are more sensitive and specific, and less variable, than current assessment tools—including biomarkers such as serum creatine—across all types of kidney transplant rejection. Natera has developed its cfDNA technology for approval in the clinical setting in order to provide patients with tools for early, clinically meaningful rejection assessment. As such, Natera was awarded approval for coverage by Medicare.

4. Natera's cfDNA platform is the product of well over a decade of hard work and investment of, on average, more than fifty million dollars per year in research and development. Natera has expended substantial resources researching and developing its technologies and establishing its reputation among physicians, insurers, and regulators as a company committed to sound science and consistently accurate, reliable results. This research, and the resulting technological innovations therefrom, are protected by a substantial patent portfolio, with over 200 patents issued or pending worldwide.

5. Among these patented inventions are U.S. Patent No. 10,526,658 (the "'658 patent") and U.S. Patent No. 10,597,724 (the "'724 patent"), each of which CareDx infringes. In

its efforts to improve upon the standard of care in the transplant space, Natera has leveraged its own technologies such as the inventions disclosed and claimed in the '658 patent and '724 patent. By contrast, CareDx has used Natera's patented cfDNA technology without permission and in violation of the patent laws, while asserting only the patents of others (e.g., Stanford) to create the false impression that it is a true innovator. CareDx must be held accountable for its infringement.

6. Natera is the legal owner by assignment of the '658 patent, which was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on January 7, 2020.

7. Natera is the legal owner by assignment of the '724 patent, which was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on March 24, 2020.

8. Natera seeks monetary damages and injunctive relief to address ongoing infringement by CareDx of its valuable patents.

THE PARTIES

9. Natera is a Delaware corporation with its principal place of business at 201 Industrial Road, Suite 410, San Carlos, California 94070.

10. CareDx is a Delaware corporation with its principal place of business at 3260 Bayshore Boulevard, Brisbane, California 94005.

JURISDICTION AND VENUE

11. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 1 *et seq*.

12. This Court has subject matter jurisdiction over the matters asserted herein under 28 U.S.C. §§ 1331 and 1338(a).

13. CareDx is subject to this Court's personal jurisdiction at least because CareDx is a Delaware corporation, and because CareDx filed its own actions against Natera, Case Nos. 19-cv-00567-CFC-CJB and 19-cv-00662-CFC-CJB, in this District.

14. In addition, CareDx is subject to this Court's personal jurisdiction because, on information and belief, CareDx, directly or indirectly, uses, offers for sale, and/or sells AlloSure and other related or similar products throughout the United States and within this District. CareDx has infringed and continues to infringe Natera's patents in this District by, among other things, engaging in infringing conduct within and directed at or from this District and purposely and voluntarily placing its infringing products, including AlloSure and others, into the stream of commerce with the expectation that the infringing products will be used in this District.

15. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b). As discussed above, CareDx is incorporated in this District and thus resides in this District.

FACTUAL BACKGROUND

Natera's History of Innovation

16. Since 2004, Natera has been a global leader in genetic testing, diagnostics, and DNA testing, including cfDNA testing. Natera's mission is to improve the management of disease worldwide and focuses on reproductive health, oncology, and organ transplantation. To improve the management of these conditions, Natera has developed novel technologies to make significant and accurate clinical assessments from the miniscule amounts of cfDNA present in a single blood sample. These technologies include methods to manipulate cfDNA in unconventional ways in order to capture information about genetic variations ("polymorphisms") in cfDNA and usefully transform that information for noninvasive testing. Natera develops and commercializes its own innovative, non-traditional methods for manipulating and analyzing

cfDNA, and offers a host of proprietary cfDNA genetic testing services to the public to assist patients and doctors to evaluate and track critical health concerns.

17. Since its founding, Natera has researched, developed, and released ten molecular tests with applications in prenatal diagnostics, cancer, and organ transplants, many of which are available through major health plans, or covered by Medicare or Medicaid, and therefore available to most patients in need of those tests. Natera's tests have helped more than two million individuals to date. Natera's robust laboratory now processes tens of thousands of tests per month from the United States and internationally, improving the ability of physicians to monitor and manage crucial health issues and patients to prosper around the world.

18. Building on these innovations, in 2019 Natera launched its patented next-generation cfDNA diagnostic test for evaluating organ transplant health called "Prospera." Prospera is designed to be, and is, the most precise medical testing regime for early, clinically meaningful transplant rejection assessment. Prospera assesses the risk of transplant rejection with greater precision than the existing standard of care. Earlier tools for diagnosing organ transplant rejection are either invasive or inaccurate. Prospera was created to help physicians improve transplant survival by enabling them to optimally suppress immune-system-mediated rejection in transplant recipients while avoiding unnecessary and invasive biopsies of the transplanted organ itself.

19. Prospera has been clinically and analytically validated for performance over all donor types, rejection types, and clinical presentations. Prospera also is the first diagnostic test with high sensitivity to both T-cell mediated and antibody mediated rejection. Prospera's unique ability to identify T-cell mediated rejection ("TCMR") gives a more comprehensive view of a patient's rejection status. Prospera also is the first transplant test to publish the detection of

subclinical rejection, which occurs in 20-25% of patients in the first two years post-transplant, and is considered a major driver of transplant failure.

20. Prospera's validation led Medicare to issue a draft Local Coverage Determination ("LCD") for Prospera in March 2019. In its draft LCD, Medicare determined that "[t]he evidence is sufficient to support that Prospera provides a non-invasive assessment tool to assess for the presence of active allograft rejection." Furthermore, the LCD established that the "evidence also supports that Prospera identifies both ABMR [antibody-mediated rejection] and TCMR [T-cell mediated rejection], and it is validated to detect subclinical AR [active rejection]." The LCD was finalized after receiving overwhelming public support, with the vast majority of public comments being positive. Natera received nearly four times as many supportive letters than not. In fact, the only three letters submitted which did not support the coverage were submitted either by CareDx itself, by self-identified paid advocates of CareDx or, on information and belief, by known CareDx advisors—all in an attempt by CareDx to interfere with Natera's commercialization efforts.

21. Natera's history of and dedication to innovation in the analysis and testing of cfDNA has resulted in a world-class patent portfolio, with over 86 patents issued to date. Natera has well over 100 additional patent applications currently under review before the United States Patent & Trademark Office ("USPTO") and other patent offices around the world.

CareDx

22. CareDx is a molecular diagnostics company that develops and commercializes testing products for transplant recipients.

23. CareDx markets and sells its own transplant diagnostic products including, among others, AlloSure, AlloSure Heart, AlloSure Kidney, KidneyCare, HeartCare, and AlloSeq cfDNA (the "CareDx Products").

24. On information and belief, AlloSure and at least the other CareDx Products infringe the '658 patent and the '724 patent. These patents cover innovative, non-traditional methods for manipulating and measuring DNA from a first individual in a biological sample of a second individual. As set forth below, CareDx's infringing products incorporate or use technology that is protected by the '658 and '724 patents owned by Natera. CareDx has used Natera's patented technology without payment or permission.

The '658 Patent

25. The '658 patent, issued on January 7, 2020, is titled "Methods for Simultaneous Amplification of Target Loci." Joshua Babiarz, Tudor Pompiliu Constantin, Lane A. Eubank, George Gemelos, Matthew Micah Hill, Huseyin Eser Kirkizlar, Matthew Rabinowitz, Onur Sakarya, Styrmir Sigurjonsson, and Bernhard Zimmerman are the named inventors, and they invented this technology as part of Natera's innovative research team. Natera is the original and current owner by assignment of the '658 patent. A true and correct copy of the '658 patent is attached hereto as Exhibit A.

26. Claim 1 of the '658 patent recites:

> 1. A method for measuring an amount of DNA from a first individual in a biological sample of a second individual, comprising:
>
> pre-amplifying at least 50 polymorphic loci from cell-free DNA of mixed origin in a single reaction volume to obtain pre-amplified DNA, wherein the cell-free DNA is extracted from the biological sample and comprises DNA

from the first individual and DNA from the second individual, wherein neither the first individual nor the second individual is a fetus;

dividing the pre-amplified DNA into multiple aliquots; amplifying subpools of the polymorphic loci in parallel in individual reaction volumes to obtain amplified DNA, wherein each reaction volume comprises at least one aliquot of the pre-amplified DNA; and pooling the amplified DNA into one pool;

sequencing the amplified DNA by high-throughput sequencing and measuring an amount of each allele at the polymorphic loci; and

determining the amount of the DNA from the first individual in the biological sample using the amount of each allele at the polymorphic loci.

27. The claims of the ’658 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to measuring DNA in a sample using synthetic pieces of DNA, including amplification products, which are produced using synthetic tools such as primers, to provide a novel and innovative solution to problems peculiar to the particular problem of amplifying and measuring small amounts of DNA from one individual or organism in a biological sample of another individual or organism. The ’658 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area. Attached hereto as Exhibit F is the Declaration of Professor John Quackenbush, Ph.D., which is incorporated here by reference, who further details the technological background of the ’658 patent and documents its inventive nature, including its incorporation of an inventive concept.

The '724 Patent

28. The '724 patent, issued on March 24, 2020, is titled "System and Method for Cleaning Noisy Genetic Data from Target Individuals Using Genetic Data from Genetically Related Individuals." Matthew Rabinowitz, Milena Banjevic, Zachary Demko, and David Johnson are the named inventors, and they invented this technology as part of Natera's innovative research team. Natera is the original and current owner by assignment of the '724 patent. A true and correct copy of the '724 patent is attached hereto as Exhibit G.

29. Claim 1 of the '724 patent recites:

> 1. A method for determining genetic data for DNA from a first individual in a biological sample of a second individual, the method comprising:
>
> (a) amplifying a plurality of polymorphic loci on cell-free DNA extracted from the biological sample to generate amplified products;
>
> (b) measuring an amount of the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of polymorphic loci;
>
> (c) determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of polymorphic loci.

30. The claims of the '724 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to an unconventional method for determining genetic data for DNA from a first individual in a biological sample of a second individual using synthetic pieces of DNA, including amplification products, which are produced using synthetic tools to provide a novel and innovative solution to amplifying and measuring small amounts of DNA from one individual or organism in a biological sample of another individual or organism.

CareDx's Infringing Acts

31. The allegations provided below are exemplary and without prejudice to Natera's infringement contentions. In providing these allegations, Natera does not convey or imply any particular claim constructions or the precise scope of the claims. Natera's claim construction contentions regarding the meaning and scope of the claim terms will be provided under the Court's scheduling order and local rules.

32. The infringing products include, but are not limited to, the CareDx Products and any other infringing method, product, device, or test developed by CareDx.

33. As provided in more detail below, each element of at least one claim of each of the '658 and '724 patents is literally present in the CareDx Products or is literally practiced by the processes through which the CareDx Products are practiced. To the extent that any element is not literally present or practiced, each such element is present or practiced under the doctrine of equivalents.

34. On information and belief, CareDx released its AlloSure product for kidney transplant recipients to the public in 2017.

35. Prior to that release, on November 6, 2016, CareDx—through Grskovic, *et al.*—published a paper in the Journal of Molecular Diagnostics, titled Validation of a Clinical-Grade Assay to Measure Donor-Derived Cell-Free DNA in Solid Organ Transplant Recipients, Vol. 18, No. 6, pp. 890-902, attached hereto as Exhibit B. As indicated by CareDx's AlloSure website under Sample Preparation (http://www.allosure.com/sample-preparation/), this paper describes CareDx's AlloSure test and methodology. *See* Exhibit C at 1 (Sample Preparation) ("The test design, development, and validation are described in Grskovic et al., J Mol Diagn, 2016.").

36. Performance of CareDx's AlloSure test, and all variants thereof, and all CareDx Products using similar technology, infringe at least one claim of the '658 patent in the following

ways. AlloSure, and any other CareDx Product that employs similar technology, determines genetic data regarding, or measures, cfDNA from a transplant donor in a biological sample of a transplant recipient. This is based on targeted amplification of at least 266 single nucleotide polymorphisms ("SNPs") in cfDNA extracted from the transplant recipient's blood to generate amplified products. The at least 266 SNPs in the cfDNA are preamplified in a single multiplex reaction. The preamplified material is divided into multiple aliquots and further amplified using 48 limited complexity multiplexes with 1 to 11 targets per reaction. Index sequences and Illumina sequencing adapters are added to each sample DNA by polymerase chain reaction ("PCR"), and up to 16 amplified samples are pooled in equimolar amounts, and then sequenced with high-throughput sequencing by synthesis on an Illumina Mi-Seq. The amounts of amplified products are measured by this sequencing by synthesis. The sequencing data are then used to measure the amount of amplified products, including each allele at the polymorphic loci to obtain genetic data at the plurality of polymorphic loci and determine the amount of donor-derived cfDNA in the sample.

37. As an example, attached hereto as Exhibit D is a preliminary and exemplary claim chart detailing CareDx's infringement of the '658 patent. Exhibit D is not intended to limit Natera's right to modify this chart or any other claim chart or allege that other activities of CareDx infringe the identified claims or any other claims of the '658 patent or any other patents.

38. Performance of CareDx's AlloSure test, and all variants thereof, and all CareDx Products using similar technology, also infringe at least one claim of the '724 patent in the following ways. AlloSure, and any other CareDx Product that employs similar technology, determines genetic data for DNA from a first individual in a biological sample of a second individual. This is based on amplifying a plurality of polymorphic loci, or SNPs, on cell-free

DNA extracted from the biological sample by PCR to generate amplified products. AlloSure measures an amount of the amplified products by sequencing-by-synthesis on Illumina sequencing instruments such as MiSeq to obtain genetic data at the plurality of polymorphic loci. AlloSure then determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of polymorphic loci, in that the donor-derived cfDNA (most likely genetic data for DNA from the first individual) was determined from the background-corrected alternate allele frequencies of the recipient homozygous SNPs.

39. As an example, attached hereto as Exhibit H is a preliminary and exemplary claim chart detailing CareDx's infringement of the '724 patent. Exhibit H is not intended to limit Natera's right to modify this chart or any other claim chart or allege that other activities of CareDx infringe the identified claims or any other claims of the '724 patent or any other patents.

40. CareDx has thus made extensive use of Natera's patented technology, including the technology described and claimed in the '658 and '724 patents. Natera has no choice but to defend its proprietary and patented technology. Natera thus requests that this Court award it damages sufficient to compensate for CareDx's infringement of the '658 and '724 patents, find this case exceptional and award Natera its attorneys' fees and costs, and grant an injunction against CareDx to prevent ongoing infringement of the '658 and '724 patents.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 10,526,658

41. Natera incorporates by reference and re-alleges the foregoing paragraphs as if fully set forth herein.

42. On information and belief, CareDx has infringed and continues to infringe the '658 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing, selling, or offering for sale within the United States without authority the AlloSure test and all other CareDx Products using similar technology. As an example, attached as Exhibit

D is a preliminary and exemplary claim chart detailing CareDx's infringement of the '658 patent. This chart is not intended to limit Natera's right to modify the chart or allege that other activities of CareDx infringe the identified claims or any other claims of the '658 patent or any other patents.

43. Exhibit D is hereby incorporated by reference in its entirety. Each claim element in Exhibit D that is mapped to the AlloSure test is an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT II: INFRINGEMENT OF U.S. PATENT NO. 10,597,724

44. Natera incorporates by reference and re-alleges the foregoing paragraphs as if fully set forth herein.

45. On information and belief, CareDx has infringed and continues to infringe the '724 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing, selling, or offering for sale within the United States without authority the AlloSure test and all other CareDx Products using similar technology. As an example, attached as Exhibit H is a preliminary and exemplary claim chart detailing CareDx's infringement of the '724 patent. This chart is not intended to limit Natera's right to modify the chart or allege that other activities of CareDx infringe the identified claims or any other claims of the '724 patent or any other patents.

46. Exhibit H is hereby incorporated by reference in its entirety. Each claim element in Exhibit H that is mapped to the exemplary AlloSure test is an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

PRAYER FOR RELIEF

WHEREFORE, Natera respectfully requests the following relief:

1. A judgment that CareDx has infringed the ’658 patent, directly and indirectly, literally or under the doctrine of equivalents;
2. A judgment that CareDx has infringed the ’724 patent, directly and indirectly, literally or under the doctrine of equivalents;
3. An order preliminarily and permanently enjoining CareDx and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting on behalf of or in active concert or participation therewith, from further infringement of the ’658 patent;
4. An order preliminarily and permanently enjoining CareDx and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting on behalf of or in active concert or participation therewith, from further infringement of the ’724 patent;
5. An award of damages sufficient to compensate Natera for CareDx’s infringement under 35 U.S.C. § 284;
6. A determination that this is an exceptional case under 35 U.S.C. § 285 and that Natera be awarded attorneys’ fees;
7. Costs and expenses in this action;
8. An award of prejudgment and post-judgment interest; and
9. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

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March 25, 2020

CERTIFICATE OF SERVICE

I hereby certify that on March 25, 2020, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on March 25, 2020, upon the following in the manner indicated:

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